REMARKS

Claims 1-21 are pending. Claims 1-8, 11-15, and 18-21 stand withdrawn (note that the Office Action Summary is in error, and fails to note that claims 11-14 are withdrawn from consideration).

Claim 16 (as well as withdrawn claims 12 & 13) is amended to correct a typographic error introduced in the Second Preliminary Amendment. The groups listed for R' in the claim are now the same as those originally presented.

Favorable reconsideration is requested in view of the following.

Enablement

Claims 16 and 17 stand rejected under the enablement requirement. Applicants traverse the rejection. The specification, taken together with the art, enables the claimed invention.

Claim 16 recites, *inter alia*, a "pharmaceutical composition comprising: a therapeutically effective quantity of at least one compound of formula (II) ... in combination with at least one pharmaceutically acceptable vehicle." Claim 17 depends from Claim 16 and limits the structure of the compound.

The rejection questions whether results obtained using an *in vivo* mouse model correlate to humans, and whether the instant yeast-based assay correlates with prion mouse models or with humans suffering from prion diseases.

The facts in this case are similar to those in *Cross v. Iizuka*, where the Federal Circuit found it significant that "in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween." *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed.

Cir. 1985). The court continued: "based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Id.*; MPEP 2164.02

Furthermore, the Board has held that even in a highly unpredictable art, concrete guidance in the form of working examples (such as provided in this case) weighs strongly in finding enablement. *Ex parte Gleave*, 84 USPQ2d 1681, 1689 (Bd. Pat. App. & Int. 2006).

Applicants respectfully submit that the rejection has misplaced emphasis on applicability to humans with regard to the claimed pharmaceutical composition. One of ordinary skill in the art would have understood that the claimed "therapeutically effective quantity" includes effectiveness in animals. For example, the specification recites "administering to an animal or to a patient a therapeutically effective quantity ..." (Specification, ¶0058).

In this case, direct evidence supports the notion that the disclosure is sufficiently enabling of the rejected claims. Namely, "the vast majority of drugs" isolated using a yeast-based assay (corresponding to that described in the present specification) "turned out to be active ... in vivo in animal models." Tribouillard *et al.*, Prion 1:1, 48-52 (2007) at page 51 (this reference was cited in the IDS dated November 12, 2008). This strong correlation between activity in the yeast system and activity *in vivo* provides more than the "reasonable correlation" required by law between *in vitro* and *in vivo* results.

Furthermore, Example 7 of the present specification validated the screening method with known drug compounds (including those found by the Nobel Laureate Stanley Prusiner), and found that the compounds exhibited good correlation between mammalian and yeast systems (Specification, ¶¶ 0110 - 0114). This correlation is further evidence the claims are enabled.

The rejection maintains that Barret (2003) found no curative effect of quinacrine in mice. The studies described in Barret relate to discerning the mechanism of action of quinacrine and its specific potential utility during a treatment strategy. The authors concluded that "we therefore propose that quinacrine can interact with PrP to inhibit PrPres formation but that it is unable to significantly disrupt preformed aggregates and therefore has a limited role in therapeutic interventions during the late stages of prion diseases" (p. 8463, left column). Stated differently, quinacrine is a relevant candidate for prion disease therapy, but not in the late stages of the disease. Thanks to the different models, the precise utility of quinacrine and specific strategies of treatment may be established for quinacrine, which is a medication that is presently used for treating prion disease (see Geschwind et al.).

The rejection further notes that Groschup states that factors which modulate the pathogenesis of prior infection in vivo remain enigmatic. However, many diseases are treated despite their pathogenesis being an enigma. It is not necessary to understand all the features of a disease to treat it, and the knowledge of all such features is not a legal requirement for enablement. While Groschup notes that transgenic mice are not bona fide models for the prion pathogenesis in humans and animals, it also states that they can be used to make better exposure and

transmission risk assessment for human and animals. Enablement requires that one skilled in the art be able to make and use the claimed invention without undue experimentation -- there is no obligation to determine the pathogenesis of a disease to obtain a patent on a pharmaceutical composition. MPEP 2164.

The rejection asserts that "6AP is not among the genus" of claimed compounds. Applicants respectfully disagree. 6AP (structure shown on p. 3 of Tribouillard-Tanvier et al., PLoS ONE; Vol. 3, Issue 5, e2174 (2008), already of record) corresponds to a compound of formula (II) wherein p and n are each 0 and R' is NH_2.

Regarding Zhou (2004), the rejection cites a sentence stating that caution must be exercised in equating the phenotype produced in an animal model with that of the modeled human disease. However, Zhou is directed at propagation rather than therapy, and the remainder of the reference is laudatory with regard to the usefulness and value of models. For example, stating that "models have been an invaluable tool" and "cell models have provided considerable information." Zhou, p. 159, col. 2. Zhou also notes that "models have provided investigators with great opportunities to study human prior diseases at molecular, cellular and animal levels *in vitro* and *in vivo*." Zhou, p. 161, col. 2. Zhou thus supports the use of models as enabling the study of prions and related therapies.

Moreover, it is unreasonable to require testing on human patients at the early stages of drug discovery, and models must be used instead. The law recognizes that an applicant need not have actually reduced the invention to practice prior to filing. MPEP 2164.02. Indeed, ethical and legal considerations *require* that animal and other models be used before providing a new drug to humans. Furthermore,

assays in patients often begin about ten years following drug discovery, and to require applicants to delay filing for such a period would be unduly prejudicial.

For all of these reasons, Applicants respectfully traverse the enablement rejection and request reconsideration and withdrawal thereof.

Double Patenting

Claim 16 was provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same subject matter as claim 19 of copending Application No. 11/483,822 ("the '822 application").

Claims 16 and 17 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 9, 10, and 17 of the '822 application.

A Terminal Disclaimer is filed herewith, thereby obviating these rejections.

Conclusion

For at least the reasons stated above, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections, and to allow the present application.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned attorney so that prosecution of the application may be expedited.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

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